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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/824,468	04/02/2001	Arthur M. Krieg	C1039/7049(HCL/MAT)	9046

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WOLF GREENFIELD & SACKS, PC
FEDERAL RESERVE PLAZA
600 ATLANTIC AVENUE
BOSTON, MA 02210-2211

EXAMINER	
BLANCHARD, DAVID J	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 10/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/824,468	KRIEG ET AL.	
	Examiner	Art Unit	
	David J Blanchard	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 July 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-32 and 34-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-32 and 34-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-21 and 33 are cancelled.

Claims 22-23, 32, 36 and 38 have been amended.

2. Claims 22-32 and 34-43 are pending and under examination.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. This Office Action contains New Grounds of Rejections.

Objections/Rejections Withdrawn

5. The objection to the specification for not containing the patent numbers for USSNs 08/960,774 and 08/738,652 is withdrawn in view of the amendments to the specification.

6. The rejections of claims 22-24, 26-30 and 32-34, parts a and b, under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention are withdrawn in view of the Applicant's arguments and amendments to the claims.

7. The rejection of claim 32 under 35 U.S.C. 102(a) as being anticipated by Chace et al as evidenced by Krieg A. M. is withdrawn in view of the amendment to the claim.

8. The rejection of claims 22-32 and 34-43 under 35 U.S.C. 103(a) as being unpatentable over Chace et al as evidenced by Krieg A. M. [A] in view of Krieg et al [B] and Maecker et al is withdrawn in view of the amendments to the claims.

9. The rejection of claims 22-32 and 34-43 under 35 U.S.C. 103(a) as being unpatentable over Krieg et al in view of Gately et al and Ballas et al and Noll et al and Levy et al is withdrawn in view of the amendments to the claims.

New Grounds of Rejection/Response to Arguments

10. Claims 22-32 and 34-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Krieg et al (U.S. Patent 6,207,646 B1, 2/7/1995) in view of Pulaski et al (Cancer Research, 53:2112-2117, 1993) and Korenaga et al (Parasitology Research, 82:108-113, 1996) and Levy et al (U.S. Patent 6,099,846, 102(e) date 4/14/1995).

The claims are drawn to a composition comprising IL-3 and a CpG oligonucleotide, wherein the composition may optionally comprise an antigen selected from a tumor antigen, a microbial antigen or an allergen and a method for stimulating an immune response wherein the antigen and cytokine may be and antigen-cytokine fusion protein, a method for activating a dendritic cell and a method for treating a subject having a neoplastic disorder comprising administering said composition.

Krieg et al teach immunostimulatory nucleic acid molecules comprising the formula 5' X_1CGX_2 3' that are at least 8 nucleotides in length and can be used to treat, prevent or ameliorate a tumor or cancer, a viral, a fungal, a bacterial or parasitic infection in an individual and can be administered in conjunction with a vaccine, which is minimally comprised of an antigen (see columns 6 and 33). Krieg et al teach that the immunostimulatory CpG oligonucleotides may be administered in conjunction with an allergen to a subject to treat or prevent an allergy (see column 6, lines 62-65, and

column 34, lines 16-26). Krieg et al teach that CpG oligonucleotides act as immunostimulatory adjuvants, which can directly activate B cells, monocytic cells (including macrophages and dendritic cells) and NK cells (see Fig. 6) and IL-3 as well as numerous other cytokines are secreted by an increased number of spleen cells in response to CpG oligonucleotides and CpG containing immunostimulatory nucleic acid molecules can be administered to a subject in conjunction with a vaccine (minimally comprised of an antigen) to boost a subject's immune system and thereby effect a better response from the vaccine (see column 33, lines 28-48). Krieg et al teach subjects that are non-human animals including a dog, cat, horse, cow, pig, sheep, goat, chicken, monkey, rat, mouse, ect. (see column 13, lines 27-29).

Pulaski et al and teach that IL-3 aids in the generation of anti-tumor CTL and IL-3 stimulates the production of cytokines such as IL-2 and IL-4, which are thought to enhance antigen-presenting cell function and cytokines mediate "cross-talk" between nonspecific and specific effectors important in the antitumor response (see page 2115, right column). Pulaski et al teach that the finding that IL-3 aids in the generation of anti-tumor CTL may ultimately be important when designing therapies or vaccines to specifically enhance particular subsets of effectors such as CTL (see page 2117).

Korenaga et al teach that IL-3 acts synergistically with IL-4 in mast-cell hyperplasia (see page 112, left column and Fig. 7) and the host-defense up-regulated by IL-3 was not inhibited by the injection of anti-IL-4 or anti-IL-5 antibodies.

Levy et al teach tumor associated antigen-cytokine fusion proteins, which elicit immune responses, which are protective with respect to tumor proliferation and prolong survival time (see column 1, lines 47-52 and column 3 and Figure 8).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a composition comprising IL-3 and a CpG oligonucleotide and a method for stimulating an immune response, a method for activating a dendritic cell and a method for treating a neoplastic disorder comprising administering said composition.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a composition comprising IL-3 and a CpG oligonucleotide and a method for stimulating an immune response, a method for activating a dendritic cell and a method for treating a neoplastic disorder comprising administering said composition in view of Krieg et al and Pulaski et al and Korenaga et al and Levy et al because Krieg et al teach CpG oligonucleotides as adjuvants for amplifying an immune response to antigens of interest (i.e., vaccine compositions) and IL-3 as well as numerous other cytokines are secreted by an increased number of spleen cells in response to CpG oligonucleotides and Pulaski et al teach that IL-3 stimulates the production of IL-2 and IL-4, which are thought to enhance antigen-presenting cell function and Korenaga et al teach that IL-3 as an adjuvant acts synergistically with another adjuvant such as IL-4 and the host-defense up-regulated by IL-3 was not inhibited by the injection of anti-IL-4 or anti-IL-5 antibodies and Levy et al teach tumor associated antigen-cytokine fusion proteins, which elicit immune responses

to antigens of interest. Therefore, a person of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to combine IL-3 and a CpG olgonucleotide and use this resultant composition as a more effective adjuvant for producing an amplified immune response against an antigen of interest, that is greater than the sum of the individual effects of either IL-3 or a CpG oligonucleotide alone given that even though IL-3 and IL-4 have separate mechanisms of immune stimulation (i.e., the IL-3 response is not inhibited by anti-IL-4 antibodies), IL-3 acts synergistically with other adjuvants such as IL-4 and both IL-3 and CpG would compliment one another in amplifying immune responses to antigens of interest. Thus, it would have been obvious to one skilled in the art to have produced a composition comprising IL-3 and a CpG oligonucleotide and a method for stimulating an immune response, a method for activating a dendritic cell and a method for treating a neoplastic disorder comprising administering said composition in view of Krieg et al and Pulaski et al and Korenaga et al and Levy et al.

It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to form a third composition that is to be used for the very same purpose, idea of combining them flows logically from their having been individually taught in the prior art. In re Kerkhoven, 205 USPQ 1069, CCPA 1980. See MPEP 2144.06.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

11. The response filed 7/29/2004 has been carefully considered, but is deemed not to be persuasive. The response argues that the cited references fail to provide any motivation to combine their disclosures in order to obtain the presently claimed invention and do not provide any expectation for obtaining the claimed synergistic combination of an IL-3 cytokine and a CpG oligonucleotide. The response also argues that the analysis of *In re Kerkhoven* does not apply to the instant claims because the compositions of the combined prior art were not simply useful for the same purpose, they were also composed of the same ingredients. Further, the response argues that the combination of detergents in *In re Kerkhoven* was not synergistic in contrast to the instant claims, which relate to a synergistic combination of IL-3 and a CpG oligonulceotide. In response to applicant's argument that there is no suggestion to combine the references for obtaining the claimed synergistic combination of IL-3 and CpG oligonucleotide, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). However, there is no requirement that a motivation to make the modification be expressly articulated. The test for combining references is what the combination of disclosures taken as a whole would suggest to one of ordinary skill in the art. In re McLaughlin, 170 USPQ 209 (CCPA 1971). References are evaluated by what they suggest to one versed in the art,

rather than by their specific disclosures. In re Bozek, 163 USPQ 545 (CCPA 1969). In the instant case, the disclosure of Krieg et al teach that CpG oligonucleotides act as immunostimulatory adjuvants, which can directly activate B cells, monocytic cells (including macrophages and dendritic cells) and NK cells (see Fig. 6) and cytokines such as IL-3 are secreted by an increased number of spleen cells in response to CpG oligonucleotides and CpG containing immunostimulatory nucleic acid molecules can be administered to a subject in conjunction with a vaccine (minimally comprised of an antigen) to boost a subject's immune system and thereby effect a better response from the vaccine (see column 33, lines 28-48). Pulaski et al teach that IL-3 aids in the generation of anti-tumor CTL and IL-3 stimulates the production of cytokines such as IL-2 and IL-4, which are thought to enhance antigen-presenting cell function and cytokines mediate "cross-talk" between nonspecific and specific effectors important in the antitumor response (see page 2115, right column). Korenaga et al teach that IL-3 acts synergistically with IL-4 in mast-cell hyperplasia (see page 112, left column and Fig. 7) and the host-defense up-regulated by IL-3 was not inhibited by the injection of anti-IL-4 or anti-IL-5 antibodies. Levy et al teach that an antigen-cytokine fusion protein is protective with respect to tumor proliferation and prolong survival time.

Given, Korenaga et al teach that IL-3 as an adjuvant acts synergistically with another adjuvant such as IL-4 and Pulaski et al teach that IL-3 stimulates the production of IL-4, the ordinary skilled artisan would be motivated and had a reasonable expectation of success to combine IL-3 with another adjuvant such as a CpG oligonucleotide in order to produce a synergistic immune response against an antigen of

interest in a subject because Krieg et al teach CpG oligonucleotides as adjuvants for amplifying an immune response to antigens of interest (i.e., vaccine compositions).

A person of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to produce the combination of IL-3 and a CpG olgonucleotide and use it as a more effective adjuvant for producing an amplified immune response against a specific antigen of interest that is greater than the sum of the individual effects of either IL-3 or the CpG oligonucleotide alone because IL-3 acts synergistically with other adjuvants and both IL-3 and CpG would compliment one another in amplifying immune responses to antigens of interest.

Additionally, with respect to the composition claims (claims 32 and 34-35) and applicant's arguments that *In re Kerkhoven* does not apply to the instant claims because the compositions of the combined prior art were not simply useful for the same purpose, they were also composed of the same ingredients and the combination of detergents in *In re Kerkhoven* was not synergistic in contrast to the instant claims, which relate to a synergistic combination of IL-3 and a CpG oligonulceotide. In response to this argument, Applicant is reminded that the intended use of the claimed composition for synergistically activating a dendritic cell is given no patentable weight. See MPEP 2111.02. Further, synergism is not a requirement for nonobviousness. The art of Krieg et al teaches that CpG oligonucleotides are useful for treating a tumor and a parasitic infection and Pulaski et al and Korenaga et al teach that IL-3 is useful for treating a tumor and a parasitic infection, respectively. *In re Kerkhoven*, is unambiguous in that "It is prima facie obvious to combine two compositions each of which is taught by the prior

art to be useful for the same purpose, in order to form a third composition which is to be used for the very same purpose... [t]he idea of combining them flows logically from their having been individually taught in the prior art." Accordingly, IL-3 and a CpG oligonucleotide, each of which have been individually taught in the prior art to be useful for the same purpose, i.e., treating a tumor or parasitic infection, it would have been prima facie obvious to combine IL-3 and a CpG oligonucleotide to treat a tumor or parasitic infection. With respect to Applicant's argument that the instantly claimed composition is not composed of the same ingredients, in *In re Crockett*, 279 F.2d 274, 276, 126 USPQ 186, 188 (CCPA 1960), where claims directed to a method and material for treating cast iron using a mixture comprising calcium carbide and magnesium oxide were held unpatentable over prior art disclosures that the aforementioned components individually promote the formation of a nodular structure in cast iron, "it would be natural to suppose that, in combination, they would produce the same effect and would supplement each other". Likewise, IL-3 and a CpG oligonucleotide individually treat a tumor and a parasitic infection and it would be natural to suppose that, in combination, they would produce the same effect and would supplement each other.

Therefore, the rejection of claims 22-32 and 34-43 under 35 U.S.C. 103(a) as being unpatentable over Kreig et al in view of Pulaski et al and Korenaga et al and Levy et al in maintained.

12. Clams 22-32 and 34-43 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-2, 4-12 and 14-

23 of U.S. Patent 6,218,371 B1 in view of Pulaski et al (Cancer Research, 53:2112-2117, 1993) and Korenaga et al (Parasitology Research, 82:108-113, 1996).

Claims 22-32 and 34-43 have been described supra. Applicant is reminded that comprising is open language and as such does not exclude other cytokines or elements from the claimed composition and methods.

Claims 1-2, 4-12 and 14-23 of U.S. Patent 6,218,371 B1 are drawn to a composition and a method for activating a dendritic cell, a method for stimulating an immune response and a method for treating a subject having a neoplastic disorder with a synergistic composition comprising GM-CSF, or IL-2, or IL-4, or IFN-gamma, and a CpG oligonucleotide, wherein the CpG oligonucleotide is at least 8 nucleotides and C is unmethylated and the cytokine is a peptide and an antigen is optionally administered, wherein the antigen is a tumor antigen, a microbial antigen, or an allergen and the cytokine may be administered as an antigen-cytokine fusion protein in the method of stimulating an immune response. The claims in U.S. Patent 6,218,371 B1 do not specifically teach a synergistic combination of IL-3 and a CpG oligonucleotide. These deficiencies are made up for in the teachings of Pulaski et al and Korenaga et al.

Pulaski et al have been described supra.

Korenaga et al have been described supra.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a composition comprising IL-3 and a CpG oligonucleotide and a method for stimulating an immune response, a

method for activating a dendritic cell and a method for treating a neoplastic disorder comprising administering said composition.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a composition comprising IL-3 and a CpG oligonucleotide and a method for stimulating an immune response, a method for activating a dendritic cell and a method for treating a neoplastic disorder comprising administering said composition in view of Pulaski et al and Korenaga et al because Pulaski et al teach that IL-3 stimulates the production of IL-2 and IL-4, which are thought to enhance antigen-presenting cell function and Korenaga et al teach that IL-3 as an adjuvant acts synergistically with another adjuvant such as IL-4 and the host-defense up-regulated by IL-3 was not inhibited by the injection of anti-IL-4 or anti-IL-5 antibodies. Thus, it would have been obvious to one skilled in the art to have produced a composition comprising IL-3 and a CpG oligonucleotide and a method for stimulating an immune response, a method for activating a dendritic cell and a method for treating a neoplastic disorder comprising administering said composition in view of Pulaski et al and Korenaga et al.

13. The response filed 7/29/2004 has been carefully considered, but is deemed not to be persuasive. The response argues that the Notice of Allowability of the parent application (USSN 09/286,098, now U.S. Patent 6,218,371) stated that "according to current policy at the PTO, in order for synergism to be enabled there must be explicit data for each of the cytokines, and that one cannot predict synergistic effects for one

molecule based on data observed for another (closely related) molecule." As an initial matter, the Examiner will not comment on the prosecution history of parent application USSN 09/286,098 (now U.S. Patent 6,218,371). Additionally, Applicant appears to be calling into question the enablement of the claimed invention as there is no evidence of record for synergism between IL-3 and a CpG oligonucleotide. In response to Applicant's argument, Korenaga et al teach that IL-3 acts synergistically with other adjuvants such as IL-4 and Pulaski et al teach that IL-3 stimulates the production of IL-2 and IL-4, which are thought to enhance antigen-presenting cell function. Thus, a person of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to produce the combination of IL-3 and a CpG olgonucleotide and use it as a more effective adjuvant for producing an amplified immune response against a specific antigen of interest that is greater than the sum of the individual effects of either IL-3 or the CpG oligonucleotide alone because IL-3 acts synergistically with other adjuvants and both IL-3 and CpG would compliment one another in amplifying immune responses to antigens of interest. Further, the claimed methods and composition recite "comprising", which is open claim language and does not exclude other cytokines such as those recited in U.S. Patent 6,218,371 B1 from the claimed methods and composition.

Therefore, the rejection of claims 22-32 and 34-43 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-2, 4-12 and 14-23 of U.S. Patent 6,218,371 B1 in view of Pulaski et al and Korenaga et al.

Conclusion

14. No claim is allowed.

15. Applicant's amendment necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at (571) 272-0787. The official fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
David J. Blanchard
571-272-0827

LARRY R. HELMS, PH.D
PRIMARY EXAMINER